Decision Memo for Intravenous Immune Globulin for Autoimmune Mucocutaneous Blistering Diseases (CAG-00109N)

Decision Summary

The Centers for Medicare and Medicaid Services has decided to issue a national coverage determination for the use of IVIg in treating biopsy-proven (1) Pemphigus Vulgaris, (2) Pemphigus Foliaceus, (3) Bullous Pemphigoid, (4) Mucous Membrane Pemphigoid (a.k.a., Cicatricial Pemphigoid), and (5) Epidermolysis Bullosa Acquisita restricted to the following patient subpopulations:

1. Patients who have failed conventional therapy. Contractors have the discretion to define what constitutes failure of conventional therapy;
2. Patients in whom conventional therapy is otherwise contraindicated. Contractors have the discretion to define what constitutes contraindications to conventional therapy; or
3. Patients with rapidly progressive disease in whom a clinical response could not be affected quickly enough using conventional agents. In such situations IVIg therapy would be given along with conventional treatment(s) and the IVIg would be used only until the conventional therapy could take effect.

In addition, IVIg therapy must be used only for short-term therapy and not as a maintenance therapy. Contractors have the discretion to decide what constitutes short-term therapy.

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Decision Memo

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Subject: Coverage Decision Memorandum for Intravenous Immunoglobulin (IVIg) for the Treatment of Autoimmune Mucocutaneous Blistering Diseases

Date: January 22, 2002

This memo serves four purposes: (1) describes autoimmune mucocutaneous blistering diseases and methods of managing these skin disorders; (2) reviews the history of Medicare's coverage of intravenous immunoglobulin (IVIg) in the management of autoimmune mucocutaneous blistering diseases; (3) presents and analyzes the relevant scientific and clinical data related to IVIg and autoimmune mucocutaneous blistering diseases; and (4) delineates the reasons for issuing a positive national coverage decision.

I. Clinical Background

Pemphigus vulgaris (PV) is a chronic disease characterized by fragile, flaccid blisters with surrounding erythema. Autoantibodies to desmoglein 3 cause splitting within the epidermis. PV can produce both cutaneous and mucosal lesions. The severity and natural history of the disease are variable. Prior to corticosteroid treatment, however, most patients with PV died.[1] Current therapy with steroids and/or immune suppressive agents has reduced the overall mortality rate to between 5-15%. Presently, opportunistic infection or complications of conventional therapies usually cause death. Disease onset is usually around the age of 50, although it can develop in younger patients.[2] PV affects men and women equally. There is a presumed genetic predisposition and the disease is more common in people of Eastern European Jewish descent.

Pemphigus foliaceus (PF) is an autoimmune condition that affects the upper layers of the epidermis. It is less severe then PV with an insidious onset that produces scattered, scaly painful lesions on the face, scalp and trunk. Blistering is not always obvious because the cleavage plane is so high in the epidermis. The disease is primarily cutaneous and mucosal lesions are uncommon. The disease itself is not life threatening and generally responds well to conventional treatments; mortality is usually linked to myocardial infarction and opportunistic infection.

Bullous pemphigoid (BP) is the most common autoimmune blistering disease with an approximate incidence of 10 cases per million population.[3] It is characterized by IgG autoantibodies to hemidesmosomes, which cause subepidermal blisters. The disease is chronic but remissions occur more frequently than with PV or PF.[4] The disease starts with pruritis and erythemateous lesions, which progress into large, tense blisters on the erythemateous and normal skin. Mucosal involvement is very common. Blisters generally do not scar. Onset of BP usually occurs after 60 years of age.[5] Untreated BP runs a chronic, generally self-limited course with disease duration usually between 3-6 years. Untreated, up to one-third of elderly patients with active, generalized disease may die. Localized disease is usually very responsive to treatment.

Mucous membrane pemphigoid (MMP), a.k.a. cicatricial pemphigoid, is a rare, chronic blistering disease of the mucosa. Any mucosal surface can be affected, however, the ocular (conjunctiva) and oral mucosa (gingiva) are most frequently involved. Ocular involvement can lead to blindness through progressive conjunctival scarring.[6] Cutaneous lesions have been reported in approximately one-third of patients. The disease, which affects more females then males, results in permanent scarring of the affected area.

Epidermolysis bullous acquisita (EBA) is the rarest of these mucocutaneous blistering diseases. It is characterized by non-inflammatory, either trauma induced or spontaneous, blisters on the acral and extensor surfaces. Usual onset is between 40 and 60 years of age. EBA is classified into three clinical subtypes: simplex in which blistering occurs at or above the basal cell level; junctional where blistering occurs at the lamina lucida level; and dystrophic where blistering occurs below the lamina densa level. Oral, conjuctival, and nasopharyngeal mucosal involvement are common. Some patients develop a nail dystrophy and alopecia. Squamous cell carcinomas often arise in patients with chronic cutaneous lesions.[7] EBA has been characterized as the most difficult autoimmune blistering disease to treat because response to treatment is varied and unpredictable.

Diagnosis of these blistering diseases is most commonly confirmed by direct immunoflourescent microscopy (IDIF). The first step of IDIF is a punch biopsy of a blister edge. The sample, which contains both intact and blistered skin, is then placed in an immunoflourescent holding medium. Using specific antibodies, the sample is analyzed to determine the presence of cutaneous antigens. Diagnosis can also be made using direct immunoelectron microscopy, immunoprecipitation, Western Blot analysis or an ELISA assay.

The most common conventional therapy for autoimmune blistering disorders is oral or intravenous corticosteroids such as prednisone with or without an immune suppressive agent, such as cyclophosphamide, azathioprine, mycophenolate mofetil. All of these conventional therapies, however, have potentially serious side effects. Steroids are associated with increased susceptibility to infection, osteoporosis, diabetes, cataracts, glaucoma, gastrointestinal problems, and psychiatric impairments, to name a few. While the immune suppressive agents act to reduce the side effects of the steroids, they all have their own potential toxicities. For example, cyclophosphamide is associated with bone marrow suppression, bladder hemorrhage, pulmonary fibrosis, and sterility. Azathioprine can cause hepatotoxicity. Dapsone, a frequently used agent, is a sulfa derivative and, hence, must be used with caution in sulfa-sensitive patients. It also has the potential to precipitate aplastic anemia. Mycophenolate mofetil, the newest of the agents, can induce an irregular heartbeat, dizziness, chest pain, blood in urine, fever, chills or sore throat, swelling of face or tongue, feet or legs, bleeding or unusual bruising, nausea, vomiting, and disrupted sleep.

Alternatives to conventional therapies, which have shown variable benefit, include plasmapheresis and extracorporeal photopheresis. These treatments have been used mainly in severe cases of pemphigus to remove the causative antibodies from the blood. Their effectiveness remains unproven.

Intravenous immunoglobulin (IVIg) is a blood product prepared from the pooled plasma of donors. Immunoglobulin was initially developed over 40 years ago as an intramuscular preparation for the prophylaxis and treatment of viral diseases and primary antibody deficiency syndromes. In the early 1980s an intravenous preparation of immunoglobulin was developed. The mode of action of IVIg, either for mucocutaneous blistering disorders or other, more established uses, is not well understood although the general thought is that IVIg helps to eliminate circulating immune complexes.

II. History of Medicare's Coverage and Timeline of Recent Activities

Presently, Medicare has no specific national coverage policy with regard to the use of IVIg in the management of autoimmune mucocutaneous blistering diseases. IVIg is a biological product under §1861(s)(2) of the Social Security Act.

Timeline of Recent Activities

In April 2001, the Centers for Medicare & Medicaid Services (CMS), formerly known as the Health Care Financing Administration, received a letter making an informal request for a national Medicare coverage determination for the use of IVIg in the management of autoimmune mucocutaneous blistering diseases from A. Razzaque Ahmed, MD of the Harvard Medical School. Dr. Ahmed specifically requested coverage for patients with pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, cicatricial pemphigoid, and epidermolysis bullosa acquisita who fail to respond to standard therapy or who have experienced severe side effects from the therapy.

In August 2001, Dr. Ahmed presented his evidence to staff at CMS and sought assistance in the preparation of a formal request. The formal request was accepted on October 29, 2001.

III. FDA Status

IVIg was first licensed in the United States in 1981. It is currently produced by six manufacturers including Alpha Therapeutic, Baxter Healthcare Corporation, Bayer Corporation, Centeon LLC, the Central Laboratory Blood Transfusion Service Swiss Red Cross, and Oesterreichishes Institut fuer Haemoderivative Ges.m.b.H (OIH). The FDA approved indications for all licensed IVIg products are:

1. Primary immunodeficiency;
2. Immune-mediated thrombocytopenia / idiopathic thrombocytopenic purpura;
3. Kawasaki syndrome;
4. Bone marrow transplantation;
5. Chronic b-cell lymphocytic leukemia; and
6. Pediatric HIV-1 infection

The use of IVIg for the treatment of autoimmune mucocutaneous blistering diseases is considered an "off-label" use.

IV. Summary of Evidence

The requestor asked for coverage of IVIg for five autoimmune mucocutaneous blistering diseases: pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, mucous membrane pemphigoid (a.k.a., cicatricial pemphigoid, oral pemphigoid, or ocular cicatricial pemphigoid), and epidermolysis bullosa acquisita. CMS sought clinical articles that addressed these diseases; only English language articles were considered. Because of the extremely low prevalence of these diseases, CMS recognized that it would be difficult to perform randomized controlled clinical trials and large case-control trials on the use of IVIg to treat patients with a mucocutaneous blistering disease. Therefore, CMS considered all clinical studies, including case reports and case series, that were published, in press, or submitted for publication at the time we accepted the request.

Twelve clinical articles were submitted to CMS by the requestor (Ahmed 2001, Ahmed and Colon 2001, Ahmed and Sami 2001, Engineer 2001, Foster 1999, Letko (submitted), Miserocchi (submitted), Sami and Ahmed (submitted), Sami, Bohl and Ahmed 2001, Sami, Bohl and Ahmed (submitted), Sami, Qureshi, and Ahmed (submitted), Sami Qureshi, and Ahmed (submitted). The study by Miserocchi looked at side effects of conventional therapies and did not involve IVIg treatment of patients with blistering disorders. It was not included for review. In addition, a Medline search was performed (keywords used: pemphigus, pemphigoid, bullous pemphigoid, cicatricial pemphigoid, ocular cicatricial pemphigoid, mucous membrane pemphigoid, epidermolysis bullosa acquisita, immunoglobulin, and IVIg). The bibliographies of retrieved articles were cross-referenced to identify additional studies. These additional measures yielded 13 articles (Becker 1995, Bewley 1996, Colonna 1998, Godard 1985, Harman 1999, Humbert 1990, Meier 1993, Messer 1995, Mohr 1995, Tappeniner 1989, Toth 1999, Wever 1996, Urcelay 1997). Finally, CMS located an article on pemphigus vulgaris that is in review for publication, Bystryn (submitted). A breakdown of articles discussing each of the five disease types is as follows:

- Pemphigus Vulgaris(PV): Ahmed, 2001, Bewley, 1996, Bystryn (submitted), Colonna 1998, Humbert, 1990, Messer, 1995, Sami and Qureshi (submitted), Wever, 1996
- Pemphigus Foliaceus(PF): Ahmed and Sami, 2001, Sami and Bhol, 2001, Sami and Quershi (submitted), Toth, 1999
- Bullous Pemphigoid (BP): Ahmed 2001, Beckers 1995, Engineer 2001, Harman 1999, Tappeiner 1989
- Mucous Membrane Pemphigoid (MMP): Ahmed and Colon, 2001, Foster, 1999, Letko (submitted), Miserocchi (submitted), Sami and Ahmed (submitted), Sami and Bohl (submitted), Urcelay, 1997.
- Epidermolysis Bullosa Acquisita (EBA): Meier, 1993, Mohr, 1995.

A.*Pemphigus Vulgaris*

A total of 11 articles addressed the use of IVIg in pemphigus vulgaris (PV). Four of these were case reports (Bewley 1996, Colonna 1998, Humbert 1990, Messer 1995), and four were case series each involving less than 10 patients (Beckers 1995, Harman 1999, Tappeiner 1989, Wever 1996). The other three articles (Ahmed 2001, Bystryn (submitted), and Sami and Quershi (submitted)) were case series studies involving 21, 12 and 15 PV patients, respectively.

Ahmed reviewed 21 patients with biopsy proven PV who were treated with IVIg. The author states that to be included in this study subjects had to have active disease and had to be non -responsive to conventional treatment (i.e. steroids with immune suppressive agents). To determine that conventional treatments were ineffective, the patients had to have been unable to achieve clinical remission after nine consecutive months of standard therapy. The dose of IVIg was 2 g/kg/cycle given over three days. This cycle was repeated initially every four weeks until the patient stopped developing new lesions (i.e., clinical control). Once clinical control was established the time between IVIg cycles was increased. The endpoint of IVIg therapy was a 16-week disease-free interval between two cycles. Patients were tapered off steroids and immune suppressing agents prior to completing IVIg taper. The number of recurrences of lesions during the course of treatment was recorded, as were the number of side effects with conventional therapies. Quality of life measurements were gathered using a questionnaire administered before IVIg treatment and then after completing IVIg therapy. In this survey patients were asked to score from one (significant effect) to five (no effect) the impact the disease and conventional treatment had on their lives.

According to the author, patients had been on conventional treatment a mean of 36.4 months (12-96 months) prior to IVIg therapy. The mean age of patients studied was 56 years (23-83 years) with 10 men and 11 women included. The mean time to achieve a clinical response with IVIg was 4.5 months (2.6-6.5 months) and the mean number of recurrences during IVIg treatment was 2.7 (0-6 recurrences). All patients were successfully tapered off steroids and immune suppressive agents. Steroid taper was achieved in a mean of 4.8 months (2.6-7.5 months), and immune suppressive agents were decreased over a mean of 2.9 months (0-6 months). After conventional agents were discontinued, IVIg was used as a monotherapy. IVIg therapy, including the time it was used in conjunction with conventional treatments, averaged 22.7 months (19.8-28 months). The time interval between the final IVIg treatment and the last follow-up visit was 20.4 months (13-73 months).

Statistical analysis demonstrated that the number of relapses and duration of steroid and immune suppressive agents was significantly shorter once IVIg therapy was started ($p<0.0001$ for each of these three variables). In addition, the patients' report of quality of life improved significantly following IVIg therapy ($p<0.0001$). The duration of therapy prior to IVIg therapy and the duration of therapy (which includes IVIg) after the start of IVIg did not show significance ($p=0.18$). Although the authors reported that autoimmune antibody levels did decrease with IVIg therapy, a detailed discussion of this finding is not provided.

Bystryn et al. treated 12 patients with PV who were unresponsive to conventional therapy. All 12 had been treated with high dose steroids for at least two-weeks immediately preceding the IVIg therapy although the length of disease prior to IVIg ranged from two months to five years. Six of the patients had also been treated with immune suppressive agents immediately preceding IVIg therapy. Cyclophosphamide or azathioprine was given concurrently with IVIg. The dose of IVIg was 400mg/kg/day for five days, and only one cycle of IVIg was given.

The authors found that within one week of IVIg administration, the activity of PV was controlled in most cases and that within two weeks the extent of skin lesions was reduced by at least 75% in 10 of the 12 subjects. In the other two subjects there was no improvement in one and "some improvement" (not defined) in the other. In addition, serum autoantibody levels declined by an average of 59% within one week of IVIg administration. The length of follow-up was not stated. The authors felt that the clinical response was not due to the concurrent administration of immune suppressive agents since in six patients they had been on the drugs before receiving IVIg and had not had a response. In the six patients who were started on cyclophosphamide or azathioprine at the same time IVIg was initiated, the authors stated that it generally takes six weeks before these immune suppressive agents demonstrate an effect, thus the quick response seen in these patients, they felt, was due to IVIg.

Sami et al provided a case series involving 15 patients with biopsy proven PV who received IVIg therapy. The 8 men and 7 women in their study had a mean age of 58 years (range not given). Their indications for IVIg therapy included failure of conventional therapies, multiple side effects of steroid therapy, and contraindications for immunosuppressive agents. They did not, however, state how long conventional treatment had to be attempted in order to qualify for IVIg. They did state, however, that the duration of conventional therapy prior to IVIg averaged 19.9 months (4-60 months). The treatment protocol was similar to that noted in the Ahmed study above.

The authors found that the duration of steroid therapy was significantly shortened with the use of IVIg (mean 19.9 months prior to IVIg and mean 4.3 after starting IVIg, $p = 0.0034$). The number of relapses was also significantly less after starting IVIg (mean 4.9 relapses prior to IVIg (range 3-7) and mean 0.7 relapses post-IVIg (range 0-3), $p<0.0001$). They note that the relapses occurring after the start of IVIg therapy occurred during a four-month period when there was a national shortage of IVIg. While they reported a number of side effects from steroid use, they do not mention any side effects from IVIg. In all 15 patients a fall in autoimmune antibody levels was observed that corresponded to control of clinical disease. The data on these antibody level changes was not provided. Finally, eight of the 15 had what the authors termed a "prolonged clinical remission," and IVIg was discontinued. These 8 patients have been followed off IVIg for a mean of 4.2 years (range not given). The other seven patients have not been weaned free of IVIg despite what the authors term "good control of their disease."

The articles by Beckers (1995), Bewley (1996), Colonna (1998), Harman (1999), Humbert (1990), Messer (1995), and Wever (1996) were small case series or case reports. While they all provided anecdotal evidence supporting the use of IVIg in PV, the inclusion criteria and treatment protocols varied. In all of these articles IVIg was used only after steroids (with or without immune suppressive agents) had failed, although the amount of time conventional therapy was tried varied widely (6 weeks to 12 years). In none of these studies was an adverse event from IVIg treatment noted.

One small case series by Tappeiner (1989) reported failure to achieve clinical remission in three PV patients using IVIg therapy. In this article, three patients with PV, ranging in duration from 1-6 months, received IVIg as primary treatment. Only one cycle of treatment was given. At the end of that cycle one patient manifested disease progression and two remained unchanged. No further cycles of IVIg were given, and the patients were switched to steroid and immune suppressive therapy. Based on this response the authors concluded that this was a therapeutic failure of IVIg in PV.

B. *Pemphigus Foliaceus*

Five articles addressed IVIg therapy in treating pemphigus foliaceus (PF). Three of these were small case series (Ahmed and Sami 2001, Sami, Bohl and Ahmed 2001, Sami, Qureshi, and Ahmed submitted for publication) while two were case reports (Beckers 1995, Toth 1999).

Ahmed's 2001 case series involved the greatest number of patients (n=11) with biopsy proven PF. The three men and eight women in this study had a mean age of 55 years (27 - 79 years). All patients had been treated unsuccessfully with steroids and/or immune suppressive agents for 16 to 45 months prior to receiving IVIg. Side effects to steroid and immune suppressive agents were noted in all 11 patients. A questionnaire was used to assess the patients' quality of life while receiving conventional and IVIg therapies. This survey used a numerical scoring system to quantify the patients' responses (1=poor quality of life to 5=high quality of life).

The dose of IVIg was 2 g/kg/cycle given over three days. This cycle was repeated initially every four weeks until the patient stopped developing new lesions (i.e., clinical control). Once clinical control was established, the time between IVIg cycles was increased. The endpoint of IVIg therapy was a 16-week disease-free interval between two cycles. All patients were weaned off of conventional therapies (over a 1.5-5.6 month period) at which point IVIg was used as monotherapy. An effective clinical response was seen in an average of 5.3 months (range 3.2 - 7.5 months) following the initiation of IVIg. All 11 patients went into a clinical remission and IVIg therapy was eventually discontinued in all subjects. The number of IVIg cycles ranged from 13 to 26 (mean 18.9), and the time during which IVIg was used as monotherapy ranged from 18.5 to 30.5 months (average 24.6 months). Side effects were reported for all patients while on conventional treatment. Reported side effects were minimal with IVIg and included headache in two patients and mild nausea in one.

Statistical data demonstrated that the number of relapses was significantly less once IVIg was initiated (3.7 prior to IVIg vs. 0.9 following IVIg, $p=0.0039$). In addition, the number of side effects was significantly reduced (average 4.7 side effects with conventional treatment vs. 0.3 with IVIg, $p<0.0010$). Finally, the patients' quality of life scores improved dramatically with IVIg therapy (average score 1.5 prior to IVIg vs. average 4.5 post-IVIg, $p<0.0010$).

Sami et al. (submitted for publication) reviewed the experience of seven patients with biopsy proven PF who had failed steroid therapy and in whom treatment with adjuvant immune suppressive agents was contraindicated. The average length of steroid therapy prior to IVIg was 2.5 years (2 months-6 years). The IVIg protocol was similar to that described for the Ahmed 2001 study discussed above. Four of the patients were men and three were women. The mean age was 54.2 years.

After beginning IVIg, all seven patients were weaned off steroids (mean 2.8 months, range 2-4 months). Thereafter, IVIg was used as monotherapy. Five of the seven were able to have the IVIg discontinued (after mean of 32.6 months, range 18-52 months) and remained in clinical remission for an average of 4.9 years (range 1.8-6.2 years). The other two patients achieved clinical remission, but needed to be maintained on IVIg at a frequency of every 10 and 12 weeks. At the time of writing this article, these two patients had been receiving IVIg for 11 and 24 months, respectively. The total number of relapses prior to IVIg therapy ranged from two to six (mean 4.1) in the subjects. Once IVIg therapy was initiated, the number of relapses ranged from 0-2 (mean 0.7). Two subjects had mild side effects with IVIg (e.g., headache and nausea). The authors report that statistical analysis showed that the duration of steroid treatment was significantly reduced with IVIg therapy ($p=0.0157$), and there were significantly fewer relapses when comparing pre- and post-IVIg treatment ($p=0.002$).

Sami et al. (2001) treated eight patients with IVIg who had biopsy proven PF. All subjects had failed conventional therapy. Four of these patients were men and four were women, and the average age was 48 years. The length of treatment prior to IVIg therapy ranged from 2 months to 6 years (average 2.5 years). Four of the patients went into remission and were tapered off IVIg after 16-19 cycles (mean 17.5 cycles). The other four patients had their disease controlled with IVIg, but were not able to be weaned from it. The authors did not state whether conventional treatments were used along side IVIg. No statistical data were presented.

The other two identified articles, Beckers 1995 and Toth 1999, were case reports involving a single patient each. Beckers' subject received conventional therapy for three weeks prior to being given IVIg. While the patient responded to IVIg, it is not clear the patient failed conventional therapy. The patient in the Toth report had progressive PF despite seven years of steroid and adjuvant immune suppressive agents. Limited follow-up data reported that after six monthly infusions of IVIg, the PF was in remission. It is unclear if IVIg was continued beyond six months.

C. *Bullous Pemphigoid*

Five studies (Ahmed 2001, Beckers 1995, Engineer 2001, Harman 1999, Tappeiner 1989) were identified that discussed the use of IVIg in treating Bullous Pemphigoid (BP). The article by Engineer et al. was a literature review, not a clinical study, and is not discussed in this memorandum. The study by Ahmed was a case series of 15 patients with biopsy-proven BP, while the Becker, Harman, and Tappeiner articles each reviewed IVIg use in two patients.

Ahmed's 2001 article included 15 patients (ten men and five women) with biopsy-proven BP who had failed treatment with both steroids and adjuvant immune suppressive agents. The mean duration of therapy prior to IVIg was 28.3 months (10 -90 months). All patients were asked to rate their quality of life on a 1-5 scale (1=poor and 5=high quality of life) before starting IVIg and at the endpoint of IVIg therapy (defined as the point when patients remained free of lesions for 16 weeks before infusion cycles). IVIg therapy was maintained until the patient could go two 16-week periods between cycles without developing new lesions.

Ahmed reported that the time to obtain effective clinical response (defined as the time required for healing of all existing lesions with lack of appearance of new lesions) ranged from two to four months (mean 2.9). The duration of IVIg therapy was 20 to 30 months (mean 24.4 months). The author stated he was able to wean all patients off IVIg (and thus all medicines). The duration of follow-up of patients off IVIg was 14 to 44 months (mean 22.9 months). The following side effects were reported with IVIg use: headache (4 patients), nausea (2 patients), and fatigue (3 patients). The number of relapses pre-IVIg therapy averaged 4.1 (range 1 to 7), while the number that occurred during IVIg treatment averaged 0.9 (range 0-3) ($p<0.0001$). Quality of life scores average 1.3 prior to IVIg and 4.6 after completing IVIg therapy ($p<0.0001$). The total duration of therapy pre- and post-IVIg did not differ significantly (average before IVIg = 28.3 months, average after IVIg treatment 24.4 months, $p=0.91$).

The articles by Beckers, Harman, and Tappeiner each provided information on two patients with BP. In the Beckers study one patient was treated with conventional therapy for only three weeks prior to trying IVIg while the length of time conventional treatment was tried prior to IVIg for the other patient was not stated. Each patient had improvement after IVIg was initiated, although a detailed protocol and follow-up information were not given. Harman also reported success with IVIg in two BP patients. These two patients were treated with conventional therapy for three and 36 months respectively. One patient received one IVIg course, and the other received three courses. A decrease in autoantibody titers was seen with each course in both patients, but the titers rose in between courses. Long-term follow-up data was not provided. As discussed in the section on PV, Tappeiner used IVIg in their two BP patients as a first line treatment, and gave one cycle of 400 mg/kg/day for five days. They saw no improvement after one course, termed it a treatment failure, and switched the patients to conventional therapy (no information on the patients' response to conventional treatment was given).

D. *Mucous Membrane Pemphigoid (a.k.a. Cicatricial Pemphigoid)*

Six articles dealing with IVIg in mucous membrane pemphigoid (MMP) were identified. One study was a non-randomized clinical trial (Sami, Bohl, and Ahmed submitted for publication), and four were case series (Ahmed 2001, Foster 1999, Letko submitted for publication, Sami and Ahmed submitted for publication). One article (Urcelay 1997) was a case report involving two MMP patients treated with IVIg. Although this case report discussed a beneficial effect from IVIg in two patients with MMP, the presented data is too sparse to draw any conclusions, and it will not be reviewed in detail.

The case series by Ahmed (2001) and by Sami, Bohl, and Ahmed (submitted) reported only on subjects with a type of MMP called oral pemphigoid. The study by Ahmed involved 20 patients with biopsy-proven oral pemphigoid followed by the author between 1994 and 2000. Of these 20 patients, 12 were treated with conventional therapies (i.e., steroids and adjuvant immune suppressive agents) and eight had a contraindication to conventional modalities and received IVIg as a first treatment. IVIg was given at a dose of 2 g/kg/cycle with cycles repeated every 4 weeks initially. IVIg was weaned according to the patients' response. As noted in previous studies, the endpoint of IVIg therapy was a 16-week disease-free interval between two cycles.

The mean age in each group was comparable (57 years in the conventional group and 58 years in the IVIg group). In addition, the duration of disease prior to the study was comparable (average 131 months in the conventional group and 122 months in the IVIg group, p = .72)). The time to initial control of the disease (defined as cessation of new lesions) was shorter in the IVIg group (average 6.1 months, range 5.3 to 7.9 months) as compared to the conventional group (average 8.5 months, range 6.5 to 11.6 months). Statistical data for this comparison was not given. The number of relapses was significantly less in the IVIg group (average 0.1, range 0-1) as compared to the conventional group (average 2.1, range 0 to 4)(p=0.001). In addition the duration of treatment was less with IVIg (average 32.9 months, range 26 to 42 months) when compared to conventional therapy (average 41.8, range 30 to 53)(p=0.008).

Sami, Bohl and Ahmed's study (submitted) included seven patients with oral pemphigoid in whom conventional therapy was contraindicated. These patients received IVIg as first-line therapy. Their report also included seven patients with oral pemphigoid who received conventional treatment. The authors stated that these seven controls were selected randomly. No information on how either the treated or untreated patients were selected was given. The IVIg protocol was similar to that described for the Ahmed study listed above. The focus of this study was to investigate the effect IVIg had on autoantibodies in oral pemphigoid. The authors did state that all seven IVIg treated patients went into a sustained clinical remission after receiving a total duration of IVIg therapy which ranged from 17 to 34 months (mean 26.9 months), but gave no data on response to treatment for the control group. They also stated that autoantibody titers decreased in both IVIg and conventional treatment groups, although the decrease was more rapid in the IVIg group. The difference in the mean rate of decline became significant at six months of therapy (p=0.03), but not before this point.

Ocular Cicatricial Pemphigoid (OCP), another type of MMP, was addressed by Foster (1999) and Letko (submitted for publication). The case series reviewed by Foster involved 10 patients (five men and five women) with biopsy-proven OCP. The patients' mean age was 74.6 years (range 56 to 81 years), and the duration of disease prior to IVIg treatment was 8.3 years (range 3 to 14 years). None of the patients responded to conventional therapy. IVIg was given every two to six weeks at a dose of 2-3 g/kg/cycle. At follow-up exam points, external ocular photographs were taken. An observer who was masked to the treatment documented the degree of conjunctivitis.

Clinical deterioration was arrested and there was resolution of the chronic conjunctivitis in all ten subjects. The masked observer's documentation of resolution of active conjunctival inflammation occurred after a minimum of 4 cycles of therapy. Four patients required 12 cycles before the disease was controlled. Conventional therapy was discontinued in all patients, although despite treatment with IVIg for 16-23 months, no patients could be weaned from IVIg. Foster noted that during a national shortage of IVIg, the dose of IVIg was reduced in each subject. All 10 patients relapsed, typically within two dose cycles.

Letko et al (submitted) presented information on eight patients with OCP who were treated with IVIg. Each of these patients had been previously treated with immune suppressive agents for MMP affecting sites other than the eye. After the diagnosis of OCP was made, therapy with IVIg was initiated. The authors compared these patients to a group of eight OCP patients who had recently been treated with conventional immune suppressive agents (historical controls). The inclusion criteria for both groups included biopsy-proven OCP, systemic conventional therapy at the time of OCP diagnosis, and a minimum of 24-months follow-up after the initiation of therapy. In the eight subjects treated with IVIg, therapy was given every two to four weeks at a dose of 2 g/kg/cycle. There was one non-masked observer who evaluated the disease severity every four to six weeks. The mean age of the patients was 62.7 years (range 52 to 70).

The initiation of treatment brought about decreased disease severity, and initiated clinical remission in both the IVIg and the historical control groups. The time to clinical remission, however, was significantly shorter for the IVIg group (average 4 months) as compared to the historical control group (average 7.5 months) ($p<0.01$). No recurrences over the 24-month follow-up were seen in the IVIg group, while five patients in the control group had at least one recurrence ($p<0.05$). At 24-months follow-up there was no active conjunctival inflammation in the IVIg patients. In the control group there was active conjunctival inflammation in three of the eight patients ($p<0.05$). Four patients had side effects directly following IVIg administration (e.g., two patients had headaches and two had nausea). There were a total of 33 side effects in the eight patients who received conventional therapy with anemia (n=14) being the most common. This difference was significant ($p<0.001$).

Sami and Ahmed (submitted for publication) reported on 15 patients with MMP who had failed conventional therapy (defined as failure to achieve a satisfactory clinical response after at least 12 months of treatment). The average age of the subjects was 66 years (range 56 to 71). All subjects suffered from involvement of multiple mucosal surfaces. IVIg was given every four weeks at a dose of 1-2 g/kg/cycle. Conventional therapies were tapered after IVIg was started. Once clinical control was reached, IVIg was also tapered, as described for previous studies. Numeric quality of life surveys were given to patients prior to IVIg initiation and at their last office visit.

Clinical control was seen on average after 4.8 months of IVIg therapy (range 2.7 to 6.4 months). The average number of relapses prior to IVIg was 7.33, while after starting IVIg, it was 1.47 ($p<0.001$). The number of side effects seen with IVIg was mild, and consisted of headache and/or nausea in seven patients. By contrast, all 15 patients had multiple side effects from conventional therapies. This difference was significant ($p<0.0001$). The quality of life score improved with IVIg therapy; average quality of life score after IVIg 4.7 and average prior to IVIg 1.6 ($p<0.0001$). The total duration of treatment prior to IVIg initiation was 77.67 months and the average duration after IVIg was started was 25.47 months. This difference was significant ($p=0.0012$).

E. *Epidermolysis Bullosa Asquisita*

Three case reports (Harman 1999, Meier 1993, Mohr 1995) were identified that addressed the use of IVIg in epidermolysis bullosa acquisita (EBA). Case reports lack a comparison group and this deficiency makes drawing conclusions from such studies difficult. Nonetheless, in an effort to review what information is available for the treatment of EBA using IVIg, a review of these three case-reports follows.

Harman reported results of IVIg use in two patients with EBA, an 18 year-old male and a 60 year-old male. The 60-year old had a four-year history of EBA that had not been responsive to conventional medical therapy. The 18 year-old had a seven-month history of medically refractory EBA. Both patients received 0.4 g/kg of IVIg per cycle given over a five-day period. Cycles were administered at first on a monthly basis and then tapered as clinically tolerated. The 18-year old received a total of six treatments and then was able to be weaned off IVIg. He remained disease-free during a four-month follow-up period. The 60-year old man had improvement in blistering. Although the cycles were tapered to every three months, he could not be weaned from IVIg.

The report by Meier reviewed the case of a 16-year-old boy who had dermatological symptoms for six years, but in whom a diagnosis of EBA was not made until seen by the author. The patient was then treated with conventional medication for two months without clinical response. IVIg was instituted (each cycle involved a dose of 400 mg/kg/day for four days) and the patient "responded almost immediately." After four cycles of IVIg (cycles given every two weeks) circulating autoantibodies were gone. No long-term data were given.

Finally, Mohr et al reported on a 55-year-old man who had been diagnosed with EBA and treated with conventional medications for three years without clinical response. IVIg was initiated (dosage the same as for the Meier case report), and the patient was continued on Dapsone (which he had been on prior). After the third cycle, there was a decrease in blister formation, and after eight cycles, the patient was weaned off Dapsone. The authors noted that new blister formation was not completely suppressed with IVIg use, and that circulating autoantibody levels were not affected after IVIg initiation. The authors did not state how long the patient was followed.

POSITION STATEMENTS AND EXPERT OPINIONS:

The American Academy of Dermatology has not issued any guidelines or position statements on the use of IVIg in these five mucocutaneous blistering disorders.

The National Pemphigus Foundation was contacted as well. They, too, have no formal position on the use of IVIg in treating pemphigus.

We also contacted experts in the field of blistering disorders. The National Pemphigus Foundation provided CMS with the names of three dermatologists who they considered to be experts in the field of blistering disorders. In addition, the dermatology branch of the National Institutes of Health was contacted. They provided CMS with two contacts in addition to the three provided by the National Pemphigus Foundation. All five experts are dermatologists at academic centers across the United States. They were contacted independent of each other. These five experts did not include the requestor or any person who had co-authored articles with him.

Uniformly, these experts felt that IVIg has a role in treating a select group of patients with PV. All of the experts stated that IVIg should only be used as short-term therapy. The ranges they gave were from one to six monthly cycles at doses not to exceed 2 g/kg/cycle. The patients that these experts felt might be eligible for IVIg included the following:

- Patients who had failed an adequate course of at least two conventional agents
- Patients who could not tolerate conventional agents because of severe side effects
- Patients with rapidly progressive disease in whom rapid control was needed. In these patients IVIg was seen as a "bridge" therapy that would be used in conjunction with conventional agents and which could affect a response while waiting for the conventional agents to take effect.

In addition, one of the experts said he uses IVIg in select patients with OCP and EBA. While the experts had limited experience in using IVIg for treating diseases other than pemphigus vulgaris (with the exception of the one investigator just mentioned), none felt it was inappropriate to use IVIg in any of the other four requested conditions as long as IVIg's use was limited to the clinical scenarios described above.

V. Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act. § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." § 1862(a)(1)(A).

Given the variety of items and services that may be covered under the Medicare program and the medical needs of our beneficiaries, the most common method of determining whether the expenses related to items and services are "reasonable and necessary" is to conduct a fact-specific inquiry on a claim-by-claim basis. In deciding claims on this basis, the beneficiary bears the burden of proving entitlement. 42 C.F.R. § 424.5(a)(6) ("The provider, supplier, or beneficiary, as appropriate, must furnish sufficient information to determine whether payment is due and the amount of payment.") On some occasions, however, the medical and scientific evidence is sufficiently compelling that the agency is able to make a national determination as to whether or not the expenses related to a particular item or service are "reasonable and necessary" for a particular population of beneficiaries with the same salient characteristics. Because NCDs are binding on Medicare contractors and administrative law judges, they often serve to obviate the need for expensive and time consuming claim-by-claim analysis.

As previously mentioned in this decision memorandum, IVIg for the treatment of autoimmune mucocutaneous blistering diseases falls within one or more Medicare benefit categories. In addition, no statutory provision specifically precludes payment. Finally, we have fully examined the medical and scientific evidence submitted with the request for a national coverage decision, and we have determined that the record currently is sufficient for the agency to make a national determination that the item or service is reasonable and necessary for a particular group of beneficiaries described below.

The available literature is comprised of case series and case reports. One study on MMP involving only oral lesions (Sami, Bohl and Ahmed, submitted for publication) stated they had a control group of MMP patients who were not treated with IVIg. Flaws in their methodology, including questions over selection of treated control subjects, make it difficult to classify this as a controlled trial.

Case series and case reports are generally considered to be of lower strength than randomized control trials, case-control or cohort studies. The lack of a comparison group in case series/reports makes it difficult to draw conclusions about a causal association between the treatment and the outcome. In many of the studies reviewed, the patients had failed extended, intensive conventional therapy. Therefore, these patients can serve as their own historical controls. Certainly having failed conventional therapy and then showing a response to IVIg is suggestive of a benefit. However, variability in the natural history of the diseases, the effect of adding IVIg to existing regimens, and inconsistencies in the regimens still create potential biases that can effect interpretation.

One of the most significant flaws noted in all of the reviewed studies is a lack of clear patient selection criteria. While many of the studies note inclusion criteria, (i.e., biopsy-proven disease and failure of conventional therapy), what, if any, exclusion criteria there were is missing from this body of literature. It is unclear whether the patients reported were all of the patients with this particular disease that the group of investigators treated. According to Dr. Ahmed, the requestor and an author on the majority of the larger case series, the published case series on PV, PF, BP, and oral pemphigus did not represent all the patients he has treated with these disorders. According to Dr. Ahmed, only patients who were on IVIg long enough to show a response were included in his case series. We asked Dr. Ahmed if he ever had treated any patient who, despite lengthy IVIg treatment, failed to respond. He said that he had two such patients, but that he had not published his experience with them. In addition, several patients started treatment but were lost to follow-up. This is a very serious flaw, and it calls into question the validity of these findings. The requestor's method of selecting patients for publication suggests that only positive treatment experiences were reported. Using such an approach (not reporting treatment failures), virtually any treatment could be shown to be 100% effective. This is especially important since his patient base makes up the bulk of the available literature. In addition, these studies do not report any serious adverse events, such as renal failure, that can occur with IVIg. Although it is possible that none of the patients in all of the studies experienced any serious adverse events, the absence of such occurrences, which have been reported in other patients with other illnesses receiving IVIg, calls into question the adequacy of reporting in these studies.

Outside of the articles authored by the requestor, there was only one case series that involved more than 10 subjects (Bystryn, submitted). This study investigated only patients with PV. There were numerous case reports and small case series (i.e., less than 10 patients). Just as with Dr. Ahmed's studies, these too suffer from potential patient selection biases, lack of a comparison group, and potential outcome assessment biases. With the exception of the study by Tappeniner (1989), the general trend was to report a benefit in using IVIg in the studied disorders. Tappeniner claimed that IVIg was not useful in treating three patients with PV and two patients with BP. They treated their patients with only one cycle of IVIg.

Another issue that the literature fails to define is the standard length of IVIg treatment. Some of the studies, most notably the case series by Bystryn et al, only used one cycle of IVIg, while many of the series by Ahmed et al used multiple cycles. Indeed, the literature is not clear if IVIg should be used as an interventional modality (i.e., short courses to affect a response and allow for adjuvant immune suppressive agents to take effect) or as maintenance therapy. Many of the experts in blistering diseases that CMS contacted, as described above, for information on IVIg therapy felt that IVIg was not appropriate as a maintenance therapy. Indeed, as noted earlier, every dermatologist considered to be an expert in blistering disorders that CMS contacted (outside of the requestor) felt that IVIg most likely has a role in treating recalcitrant cases of pemphigus vulgaris, but only in short-term courses. The consulted experts gave ranges of up to six monthly cycles as the appropriate length of IVIg treatment. Even Dr. Ahmed in one of the articles he co-authored notes the following: "A minimum dose of 2 g/kg per cycle at monthly intervals for 3 months has been the most common approach.[8]"

In many of the studies by Ahmed and co-authors, quality of life scores were reported. While these results appear impressive, the type of survey used (one question scored on a scale of 1 to 5) is a weak measure of quality of life issues. CMS has learned that this investigator's practice includes infusion clinics where patients receive extensive counseling and have access to support groups. These supportive services, while very important, need to be taken into account when a quality of life survey is administered. One cannot conclude that any perceived improvement in quality of life is due solely to the IVIg if other supportive services were involved and not taken into account.

The articles do not resolve the question of IVIg as monotherapy. While Dr. Ahmed's articles often report weaning patients off other forms of treatment, the methodologic problems discussed earlier make it difficult to conclude that this assertion is valid across the spectrum of patients with these diseases. Bystryn's case series used IVIg along with conventional immune suppressive agents. The author suggested that IVIg allowed for rapid control of the disease while allowing for these other agents to take effect. Bystryn also included patients who had not responded to immune suppressive agents alone, but responded once a bolus of IVIg was given. The rationale was that IVIg might act synergistically with conventional agents in these initially non-responsive patients. This idea of using IVIg along with immune suppressive agents was supported by many of the experts we contacted.

Certainly the low prevalence of these conditions needs to be taken into account when reviewing the literature. Bullous pemphigoid is the most common of the five diseases and it is estimated to occur in only 1/100,000 Americans. In addition, the literature suggests that only 10% of these patients fail conventional treatment. Thus, CMS estimates that even in the most common of these diseases, bullous pemphigoid, the number of patients in the U.S. that fail conventional therapy would total only approximately 300 at any one time. The number of patients with pemphigus vulgaris (estimated prevalence of 0.5/100,000) who fail conventional therapy (again, estimated at 10% of the total PV population) would be only about 150 in the U.S. at any one time. The number of patients with PF, MMP and EBA are estimated to be even lower. It is doubtful that even a multi-center study could be conducted that would draw enough patients to adequately power a clinical trial on these diseases. Thus, CMS realizes that in making a coverage determination on these diseases, we will not have the luxury of randomized-control clinical trials. It is, however, possible to document and report clinical outcomes on all treated patients, not just successes, and CMS looks forward to seeing additional studies of that type.

Although the methodologic flaws of the literature make it difficult to draw firm conclusions, the literature supports IVIg's place in treating certain patients with blistering disorders. It would be extremely difficult to perform the large well-designed clinical trials (such as randomized controlled studies) necessary to clearly demonstrate clinical effectiveness, and experts in the field uniformly support the use of IVIg in a small subpopulation of patients. Reconciling the information in the literature, and the opinions of the experts that we contacted, we conclude that the use of IVIg in treating a small, select number of patients with certain mucocutaneous blistering diseases as short-term therapy is reasonable and necessary. Although the data is strongest for PV, the similar findings for the other disorders, the similar mechanisms for tissue damage and basis for treatment across all five disorders, and the generally uniform support by experts in the field, support the use of IVIg in PF, BP, MMP, and EBA, as well. CMS would not consider this combination of clinical data, pathophysiologic data, and expert opinion adequate to support a positive national coverage decision except in cases where the number of patients with the target condition(s) is extremely small. Patients in whom the use of IVIg is supported are those who have failed treatment with at least two conventional agents after an adequate course of therapy, are unable to tolerate conventional agents because of severe side effects, or have rapidly progressive disease in whom immediate control is essential. What constitutes an adequate course will vary with the agent being tried. Side effects that might be contraindications for a patient to use conventional agents will also vary with the drug, but in general should pose a serious health risk to the patient. Patients whose disease is progressing rapidly may also benefit from a short-term course of IVIg given in concert with other immunosuppressive agents. The rationale here is that immunosuppressive agents can take a number of weeks to have an effect while IVIg can work rapidly. Thus IVIg could "bridge" these patients to the point when conventional therapy is effective. Finally, while the requestor reports using IVIg for extended periods of time, none of the contacted experts supported such long-term use nor does the scientific literature clearly support extended use. Based upon the recommendation of these dermatological experts, six months of IVIg (given at monthly intervals) was the upper limit of suggested treatment course.

VI. DECISION

The Centers for Medicare and Medicaid Services has decided to issue a national coverage determination for the use of IVIg in treating biopsy-proven (1) Pemphigus Vulgaris, (2) Pemphigus Foliaceus, (3) Bullous Pemphigoid, (4) Mucous Membrane Pemphigoid (a.k.a., Cicatricial Pemphigoid), and (5) Epidermolysis Bullosa Acquisita restricted to the following patient subpopulations:

1. Patients who have failed conventional therapy. Contractors have the discretion to define what constitutes failure of conventional therapy;

2. Patients in whom conventional therapy is otherwise contraindicated. Contractors have the discretion to define what constitutes contraindications to conventional therapy; or
3. Patients with rapidly progressive disease in whom a clinical response could not be affected quickly enough using conventional agents. In such situations IVIg therapy would be given along with conventional treatment(s) and the IVIg would be used only until the conventional therapy could take effect.

In addition, IVIg therapy must be used only for short-term therapy and not as a maintenance therapy. Contractors have the discretion to decide what constitutes short-term therapy.

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